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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PENG, BO	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 03/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/732,862	LYONS ET AL.	
	Examiner	Art Unit	
	Bo Peng	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 5/20/05.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-46 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-46 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5/20/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner of your application in the Patent and Trademark Office has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Bo Peng, Art Unit 1648.

2. This Office Action is in response to the amendment filed 20 May 2005. Claims 1, 11 and 25 are amended; Claims 1-46 are pending are under final rejection.

3. The rejections of claims 1-46 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **are withdrawn in part** in view of Applicant's amendment and arguments, and **are maintained** in part.

4. The rejections on the terms of "optionally" in part (b) of claims 1 and 11, "conservatively substituted", "substantially", "of at least about' and "up to about" in claims 1, 11 and 25 are **withdrawn** in view of Applicant's amendment and arguments.

5. The remaining rejections on claims 1, 11 and 25 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **are maintained**. Applicant's arguments have been fully considered but they are not persuasive for the following reasons:

6. Although Applicant has addressed each specific rejection and argued how the Examiner should have interpreted the claims or what Applicant has intended to claim, Applicant has not amended claims to clarify the confusing and indefinite aspects of claims 1, 11 and 25 raised in the previous Office Action. Applicant argues that one could use the examples in the specification

to define the terms in claims, such as "more stable" of claim 25. Such arguments are not persuasive. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). A claim(s) should stand on its own to particularly point out the subject matter of the invention in a way one of skill in the art could understand the invention. Moreover, the scope of claims 1, 11 and 25 is far broader than what has been taught in the specification (see discussion about rejections under 112 1st paragraph below), that one of skill in the art can not re-construct the claimed recombinant HBc chimers based on the claim language. Therefore, the rejections are maintained and affect all dependent claims.

7. The rejection of claims 1-46 under 35 U.S.C. § 112, first paragraph **is maintained**. Claims 1, 11 and 25 recite a chimer having an amino acid sequence in which up to 20% (claims 1 and 11) or 10% (claim 25) amino acids are substituted in the HBc sequence of the chimer relative to SEQ ID NO:1. As Applicant has pointed out, "these numbers and explanations are provided in the specification at pages 74 through the end of the section on page 76" (Remarks, paragraph 3, p. 24). With 20% of amino acid substitutions, Applicant specifies in the specification: "A contemplated chimer of 183 HBC residues can therefore contain up to about 36 residues that are different from those of SEQ ID NO: 1 at positions 2 through 183, and preferably about 18 residues" (page 74). The real math, however, reveals that 20% amino acid substitutions can result in may millions of possible permutations.

8. If 36 residues (or sites) are variously changed by any one of 20 amino acid residues along the HBc sequence from position 2 through 183, the number of possible change at per-mutation is

20^n, when n=36 (sites), which results in an extremely large number of variations. For example, one substitution by one of 20 amino acids would result in 20 variations; two substitutions by one of 20 amino acids at either site would result in 400 variations; three would result in 8,000 variations, etc. Thus, the scope of claims 1, 11 and 25 encompasses an extremely large number of HBc chimers that vary by 10 or 20% from SEQ ID No: 1. As a result, the claims 1, 11 and 25 read on HBc chimers with no defined structure and the specification does not reasonably convey possession of these undefined HBc chimers. Although Applicant has disclosed a few HBc chimers in the specification, Applicant has not disclosed sufficient species of alternative HBc chimers to support the broadly claimed genus of all undefined HBc chimers. Consequently, while the skilled artisan would reasonably conclude Applicant was in possession of HBc chimers, there is no indication that Applicant was in possession of all undefined HBc chimers as uncompressed by the claims.

9. Moreover, the scope of the claims must bear a reasonable correlation with the scope of enablement. See *In re Fisher*, 166 USPQ 18 24 (CCPA 1970). "It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992). Since the structural limitations of claims 1, 11 and 25 clearly cover an extremely large number of HBc chimers with undefined sequences, the specification, while being enabling for HBc chimers having SEQ ID NO: 1, does not reasonably provide enablement for making all HBc chimers with undefined structures commensurate in scope with claims 1-46.

10. Applicant argues that applicant was in possession of very large number of the desired

chimer molecules as of the filling date in view of citing references of Koschel, Zlotnick and other HBc from different strains listed in Fig. 1 of the instant specification (Remarks, p. 25). Applicant's arguments are not persuasive, because the prior art by others has been based on the specific and well known strain of HBV, and does not prove that Applicant was in possession of all undefined HBc chimers as broadly claimed.

11. In response to the aspect of the Office action that Application fails to provide necessary guidance that would lead one to such molecules (with 10 or 20% a.a substitutions), Applicant argues that in the specification Applicant has suggested use of computer programs well known in the art (for example, LASERGEN software) for guidance in determining which amino acid residues can be substituted, inserted, or deleted without abolishing biological activity or particle formation (p. 74). Applicant continues to use prior art reference to prove that it is common practice in the art of HBc chimer development. However, if such substitutions are as easy as described by Applicant simply using computer programs well known in the art, like LASERGEN software, and knowledge of the prior art, the instant invention should have been anticipated by LASERGEN technology or by prior art, since the instant invention specifically claims the substitution, deletion and insertion of amino acid residues into an HBc molecule. One of skill in the art knows that a computer program can greatly assist one in designing or predicting higher structure of a molecule. However, it still takes a research and experimentation to manipulate an HBc molecule to display foreign epitopes while maintaining its own inherent biological properties, such as capacity to form a viral capsid or viral envelope.

12. Thanks to the modern biotechnology and more than a decade of studies on HBc as a vaccine carrier by different research groups, one skilled in the art has built up a rich prior art

which provides he/her with knowledge on how to manipulate an HBc as a vaccine carrier, such as sequences and high structures of HBc, conformation of the protein, and sequence requirements for particle formation, etc. However, all those works have been done based on a few HBV strains, mostly on strain *ayw*, whose structures and functions are well studied. There is no reference indicating that the current knowledge on how to develop virus-like particles (VPL) using HBc can be readily applied to any undefined sequences, such as sequences that are 80 or 90% identical to SEQ ID NO: 1, and have reasonable expectation of success that such undefined sequences can form a stable VPL. The instant specification has not disclosed that any HBc-like sequence with 10 or 20 amino acid substitutions by any amino acids can be used and form the claimed stable HBc-like chimer. To this extent, 1970s teaching still applies: Even a single substitution can have an unpredictable effect on the conformation of the resulting molecule. "The significance of particular amino acid and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study." See Rudinger, J. at page 6.

13. Since the limitation in claims 1, 11 and 25 clearly cover a very broad range of HBc chimers with undefined amino acid sequences, in view of the empirical and unpredictable nature of the invention with regard to vaccine development, and lack of guidance and working examples in the specification, one skilled in the art cannot practice the claimed invention without undue experimentation.

14. The rejections of claims 1 and 11 under 35 U.S.C 102(b) as being anticipated by Zlotnick (1997) **are withdrawn** in view of Applicant's amendment.

15. The rejection of claim 25 under 35 U.S.C 102(b) as being anticipated by Zlotnick (1997) **is maintained**.

Applicant argues that Zlotnick's construct Cp*150 provide no insight nor suggestion about another construct, such as that claimed herein that contains an added peptide-bond epitope sequence and heterologous residues. Applicant's argument is not persuasive because claim 25 claims a recombinant HBc protein chimer molecule and Zlotnick's recombinant HBc molecule meets the limitations of claim language. It is not requirement for a 102(b) reference to provide insight or suggestion about another construct. Claim 25 claims an optional immunogenic epitope sequence in domain I [see claim 25, domain I (iv)] and one to about 50 residues of an immuogen-containing sequence at domain II [see claim 25, domain II (i)]. First, "an optional immunogenic epitope sequence in domain I" means it is not required at domain I. Secondly, HBc molecule itself contains HBc immunogens, especially on its immunodominant region of domain II, which meets the limitation of claim 25, domain II(i). Therefore, claim 25 is anticipated by Zlotnick.

16. The rejections of claims 25, 27-28, 30, 32 and 43-26 under 35 U.S.C 102(a) as being anticipated by Jegerlehner **are maintained.** Applicant's arguments have been fully considered but are not persuasive for the following reasons:

17. Applicant argues that Jegerlehner's construct has no added Cys residue at the N-terminus or C-terminus as is claimed. Applicant's argument is not persuasive because the claimed HBc chimer in claim 25 does not require Cys at either N-terminus or C-terminus. Claim 25 claims

zero to three cysteine residues at both N-terminus of domain I [see claim 25, domain I (iii)] and C-terminus of domain IV [see claim 25, domain IV (ii)], and requires that "another residue is substituted for the cysteine of position 107 at Domain III (see claim 25, domain III), 1 to about 40 residues of a linker-containing sequence at domain II [see claim 25, Domain II(a)(iii)], and said chimer molecule have at least one cysteine residue present from the recited zero to three cysteine residues of domain I and IV. Jegerlehner teaches a HBc/M2 chimer, which has zero to one cysteine in HBc domain I and IV, native Cys107 is replaced, a Gly-Gly-Lys-Gly-Gly linker-containing sequence is replaced at positions 79-80 of domain II, and finally, HBc/M2 chimer have three cysteine residues in M2 sequence present in domain II (see 2.6, column 1, p. 3106). Therefore, the instant invention is anticipated by Jegerlehner.

18. The rejections of claims 2, 4-6, 16-22, 30-39 and 43-46 under 35 U.S.C. §103, as being obvious over Zlotnick *et al.* (1997) and further in view of Pumpens (1995) **are maintained** for the following reasons:

19. Applicant argues that the rejection should be withdrawn because (1) the Office action misused Tables 1 and 3 of Pumpens' reference, because Table 1 of Pumpens' paper relates to "full length" HBc, and the Office action provides no basis for make a prediction that the stability of truncated HBc molecules are so different from full length molecules; (2) the Action has mischaracterized "a heterologous linker for a conjugated epitope present in the HBc immunodominant loop" discussed by Pumpens; and (3) Pumpens' statement that foreign insertions exert a stabilizing effect on chimeric HBcΔ is not legitimate because it is based on unpublished results.

20. First, Applicant's argument (1) that the Office action misused Tables 1 and 3 of Pumpens' reference is not found persuasive. The Office action has not misused Pumpens' reference. In fact, the Office action has recited Tables 1 through 3, not Table 1 only, to show outlining of various HBc chimers in the art, in which HBc molecules are either full-length or C-terminally truncated. While specifically pointing out the tile of Table 1 relates to "full length" HBc chimeras, not truncated chimeras as claimed invention, Applicant has forgot to point out the title of Table 3: "HBV core particles as carriers of epitopes inserted at C-terminus of full-length and C-terminally truncated HBc proteins". Therefore, the Office action has used Pumpens' reference, which covers both "full length" and "C-terminally truncated" HBc proteins, to outline various HBc chimers in the art.

21. Moreover, the Office action has not made the prediction that the stability of truncated HBc molecules is different from full-length molecules, but the prior art did. Pumpens states: "capsids formed by C-terminally truncated HBc monomers are less stable than the corresponding full-length protein particles" by referring Birnbaum 1990, Gallina, 1989 and Inada 1989. As shown, this is a statement from reference, but a prediction of the Office action.

22. Applicant argues that (2) the Action has mischaracterized a nucleotide sequence for restriction enzymes as "a heterologous linker for a conjugated epitope present in the HBc immunodominant loop" discussed by Pumpens, evidenced by Fig 2 of Borisova' paper enclosed Exhibit 5 (Remarks, paragraph 3, page 30-31). Unfortunately, the Examiner has found that it is Applicant, rather than the Office action, that has mischaracterized Pumpens' short polylinkers. Pumpens teaches: "Another specific approach involves the insertion of short polylinkers which code for minimal well-characterized epitopes, so-called immunological markers, e.g. DPAF,

necessary and sufficient for recognition by murine monoclonal antibody MA18/7 (emphasis added). Clearly, Pumpens is talking about an epitope that can be recognized by an antibody MA18/7. Consistently, in Fig. 2 of Borisova's paper enclosed Exhibit 5, the epitope polylinker, illustrated by both nucleotide acid and amino acid sequences, is inserted at positions 78 and 144 of an HBcΔ molecule. The figure of legend specifically points out "Polylinker inserted as nucleotide and corresponding peptide sequences. 'Immunological markers' presented by HBV pre-S MA18/7-recognized epitope is highlighted". After all, Pumpens' polylinker is a specific epitope, not only recognition sites for restriction enzymes as characterized by Applicant. Therefore, the Office action has not mischaracterized the reference.

23. Applicant argues (3) that Pumpens' statement that foreign insertions exert a stabilizing effect on chimeric HBcΔ lacks his legitimacy because it is based on unpublished results. Unfortunately, Applicant has mis-referenced the statement. Applicant's attention is invited to column 1, page 67 recite: "Although capsids formed by C-terminally truncated HBc monomers are less stable than the corresponding full-length protein particles [25, 44, 45],..." The statement is based on the published research by Birnbaum 1990, Gallina, 1989 and Inada 1989 (see reference Pumpens 1995).

24. Therefore, Applicant has not presented evidence to overcome the rejection under 35 U.S.C. §103, as being obvious over Zlotnick, and further in view of Pumpens.

25. The rejections of claims 7, 15 and 29 under 35 U.S.C. §103, as being unpatentable over Pumpens et al (1995) in view of Zlotnick et al. (1997) as applied to claims 1-6, 8-14, 16-28 above, and further in view of Nassal et al. (1992) **are maintained.**

26. Applicant argues that the references fail to point out adding back two cystenes at the recited position 76 and 82 of claimed HBc chimer. However, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). According to M.P.E.P. § 2143.02, "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F2d 1048, 189 USPQ 143 (CCPA 1976)."

27. It is known in the art of Biology that cysteine residues play roles to stabilize a protein conformation. As what Applicant has stated in the Remarks: "A biochemist of ordinary skill would consider the presence of cysteine residues in a protein sequence to provide added stability to the protein's 3-dimensional or tertiary structure. Should the Examiner wish evidence that the cysteines in a protein contribute a tertiary structure and stability, counsel will be pleased to provide copies of texts that so state." (Remarks, 3rd paragraph, p. 38). The Examiner thanks for the offer and fully agrees with the statement.

28. Nassal teaches the effect of internal cysteine residues of the HBc core molecule on the formation of HBc particles and stability of the protein structure. Nassal teaches that these cysteine residues are not required for the formation of the HBc particles but contribute to the stability of the overall structure of HBc protein. (see table 1, page 1022). Zheng, J. et al. (1992) performed similar studies on the disulfide bonding patterns of hepatitis B core particles.

29. One of ordinary skill in the art would have been motivated to combine the teachings of Nassal, M et al. with those of Zlotnick and Pumpens because Nassal teaches that the stepwise addition of cysteine residues to an HBc molecule can be used to tailor the stability patterns of the resultant molecule. One of ordinary skill in the art would have expected to achieve a more stable HBc chimer by tailoring the particular cysteine resides within the molecule, based upon the structural environments of the cysteine residues within the conformation of the overall HBc particle, because Nassal teaches functions/effects of these residues within the core particle. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

30. These rejections are maintained because Applicant has not presented evidence showing that there was no reasonable expectation of success.

31. The rejections of claims 2, 17, 30 and 31 under 35 U.S.C. 103(a) as being unpatentable over Nierynck et al. (1998) and Zlotnick et al (1997) **are maintained**.

32. Applicant argues that Zlotnick's construct "is not the comparison recited in the claims that recite the presence or absence of cysteins at positions 48 and/or 107" (Remarks, 1st Paragraph, page 36). Applicant's argument is not convincing, because Zlotnick's construct Cp*150 is in absence of cysteines at position 48 and 107 (Fig.1). Since Zlotnick's construct meets the claim limitation, it is comparable to the claims.

33. Moreover, in response to applicant's arguments against the Zlotnick reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208

USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

34. Neirynck teaches full-length HBc molecules are capable of incorporating a foreign epitope in its N-terminal, while Zlotnick teaches that the deletion of the C-terminal protamine domain results in an abrogation of the nucleic acid packaging while the addition of a cysteine residue to an HBc C-terminal truncation restores stability lost due to the truncation and loss of the Cys residue at position 183.

35. One of the ordinary skill in the art would have expected to achieve a C-terminal truncated HBc chimer vaccine in which contains a foreign epitope at its N-terminal, because such HBc chimer can form a stable viral particle and is free of endogenous nucleic acid binding.

36. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

37. The rejections of claims 1-6, 8-14, 16-24, 26, 31, 32-42 under 35 U.S.C. 103(a) being unpatentable over Jegerlehner as applied to claims 25, 27, 28, 30, 32 and 43-46, and further in view of Page WO 01/98333 A2 **are maintained**.

38. First, Applicant argues that the Office action has misquoted Page's statement and "the error (misquotation) was misleading and changed the intent of the disclosure". The Office acknowledges that the Action has mis-typed the Page's statement, but the error is not misleading and has not changed the disclosure. To clarify the issue, both sentences are quoted as follows:

The Office action: WO 0198333 A2 teaches "[t]he removal of the arginine repeats residues the binding of nucleic acid, whilst retention of the C-terminal cysteine allows for the formation of a stable particle." (Emphasis added)

Page: "The removal of the arginine repeats reduces the binding of nucleic acid, whilst retention of the C-terminal cysteine allows for the formation of a disulfide bond which in the native structure is important for the formation of a stable particle" (emphasis added)

In the process of the transcription, the Action mistyped "reduces" into "residues", and skipped from the use of word first "formation" to the use of word second "formation" and accidentally omitted the words in between.

39. Applicant argues that the latter error in the Action is misleading because "in the actual disclosure, the presence of the C-terminal cysteine is said to help stabilize the native molecule, whereas in the Action the cysteine was said to 'allow for the formation of a stable particle'. Those are two very different concepts in the context of this application because what may occur in the native molecule is not predictive and may or may not have an impact on a molecule having a different structure."

40. The Examiner hopes that typing errors never occur, but they do sometimes. After carefully compare the two sentences quoted above, the Examiner has found that the transcription error has not changed the concept of the statement, since the statement is about the effect of Cys residues on the formation of a stable particle through formation of a disulphide bond in native HBc structure. The Office action did not lead to "a molecule having a different structure", thus, did not change the context of Page's statement.

41. It is true that introduction of foreign residues or sequences could affect the stability of the chimer. However, it is known in the art of protein chemistry that the modifications are generally chosen so as not to destroy the conformation of the protein, and in the case of particle-forming proteins the modifications are generally chosen so as not to destroy the particle-forming ability of the protein (Jones WO 01/27281 A1, l.10, p.6). Generally, if you can keep or stabilize the native molecule while modifying the molecule, you'll have a stable particle. Thus, to stabilize

native structure of HBc molecule is a basic requirement to achieve a stable HBc chimer. Therefore, Page's statement still applies to an HBc chimer.

42. Secondly, Applicant argues that there is no such teaching as the Office action conclude "WO 01/98333 A2 teaches that HBc core molecules as epitope carriers may be made more stable by the addition of C-terminal cysteines..." (Remarks, paragraph 4, p. 37). The Examiner would like to direct Applicant's attention to WO 01/98333 A2, the summary of the invention, pp 2-3 to see recited teaching by Page.

43. Finally, to point out an unexpected result of the instant invention, Applicant states: "A key finding here is that changing two cysteines at position 48 and 107 to other residues provides enhanced stability to a claimed chimer as compared to another chimer molecule having the same sequence but also having those two native cysteines" (Remarks, p. 38). Applicant's key finding is well acknowledged. However, while arguing against the Page reference individually, Applicant has not argued that this rejection is as a combinations of references. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Jegerlehner has taught that an HBc chimer having free internal cys residues can form a stable HBc particle (see Jegerlehner, 3.1. *Gene engineering and VPL production*, column 2, p. 3106 and Fig 1, p.3107). Therefore, the instant key finding is not an unexpected and unpredicted result as Applicant argued.

44. The rejections of claims 1-46 under the judicially created doctrine of obviousness-type

double patenting as being unpatentable over (1) claims 1-78 of 09/930,915; (2) claims 1-33 of 10/274,616; (3) claims 1-53 of 10/787,734; (4) claims 98-109 of 10/806,006 and claims 79-115 of 10/806,006 **are maintained**. Applicant acknowledges the rejection and does not want to respond to it prematurely.

45. The following are new ground rejections necessitated by Applicant's amendment set forth in this Office action:

Claim Rejections - 35 USC § 112, second paragraph

46. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

47. Claim 25 (a) (i) is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

48. Claim 25 remains vague and indefinite because the term "an immuogen-containing sequence" in Claim 25 (a) (i) is indefinite, because the native sequence of HBc contains immugen-containing sequences. It is not clear if "an immugen-containing sequence" of claim 25(a)(i) means native HBc sequence or heterologous epitopes.

Remarks

49. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Bo Peng, Ph.D.

JEFFREY STUCKER
PRIMARY EXAMINER